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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/027,089	02/02/1998	FRANK H. PRORTUGAL	CAB-001	2654

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EXAMINER	
SOUAYA, JEHANNE E	
ART UNIT	**PAPER NUMBER**
1655	21

DATE MAILED: 01/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/027,089	Portugal
Examiner	**Art Unit**
Jehanne Souaya	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Oct 22, 2001 .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 19-25 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 19-25 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 20

18) ☒ Interview Summary (PTO-413) Paper No(s). 19

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Currently, claims 19-25 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Response to applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The provisional rejection of claim 25 under 35 USC 101 has been rendered moot since claims 19 and 20 of copending application 09/027,439, which claimed the same invention as claim 25 of the instant application, have been canceled in the '439 application.

4. Applicants arguments have overcome the rejection of claim 25 made under 35 USC 112, first paragraph for a lack of sufficient written description, consequently, this rejection has been withdrawn.

5. The rejection of claim 25 under 35 USC 102(f) has been rendered moot since the claims of copending application 09/027,439 which claimed the same invention as claim 25 of the instant application, have been canceled in the '439 application.

Information Disclosure Statement

6. The information disclosure statement filed Nov. 16, 2001 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Only certain entries have been considered, while those that fail to comply with the provisions of 37 CFR 1.97 have been lined through (see copy of the form provided with the office action). Those entries that have not been considered contain only a table of contents and do not contain a copy of the relevant information. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Maintained Rejections

Claim Rejections - 35 USC § 102

7. Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Cilia et al (Mol. Biol. Evol. Vol. 13, pp 451- 461, 2/26/1996) and accession number X80728.

Claim 25 is drawn to a nucleic acid probe comprising the sequence of one of SEQ ID Nos: 1-4. Accession number X80728 teaches a nucleic acid of 1385 nucleotides in length that comprises SEQ ID NO 4. The language "comprising" is considered open terminology and

encompasses sequences with any number of nucleotides on either side of the sequence in question. .

Response to Arguments

The response traverses the rejection stating that claim 25 recites nucleic acid probes capable of distinguishing certain species and that Cilia actually notes a failure to distinguish species with the sequences listed in his paper. This argument has been thoroughly reviewed but was not found persuasive. Claim 25 recites that the probe is capable of distinguishing between species of Shigella or between Shigella and E. coli in a hybridization assay. The capability of the sequence taught by Cilia, which is directed to the E. coli rrnE gene, to specifically bind to E. Coli in a hybridization assay is inherent to the sequence taught by Cilia. Nowhere does Cilia teach that this specific sequence was not capable of distinguishing between Shigella and E. coli in a hybridization assay.

8. Claim 25 is provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No.09/027,439 which has a common inventor with the instant application.

Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future patenting of the copending application 09/027,439.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 17 USPQ2d 1885 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 103

9. Claims 19-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Hammond et al (US Patent 5,374,718: Dec. 20, 1994) and Hogen (US Patent 5,714,321, 102(e) date: 2/22/94) and Dyson, N.J. (Essential Molecular Biology Vol. II: A Practical Approach, chapter 5, pages 111-156, Brown, T.A. ed. Oxford University Press, Oxford, 1992) and Anderson (Gene Probes 2: Hybridization Strategy, pp 1-29, Oxford University Press, New York, 1995) in view of Cilia et al (Mol. Biol. Evol., vol. 13, pp 451-461, 1996).

The claims are drawn to a method of discriminating between or among species of Shigella and E. coli in a sample containing organisms of one or mor taxonomic groups by selecting a probe from an operon common to two or more organisms of the taxonomic groups, wherein the probe contains one or more base mismatches and wherein the probe is capable of discriminating between organisms by hybridization at two or more wash temperatures at or above

the probes calculated or experimentally determined Tm, hybridizing the probe to the nucleic acid in the sample, and determining the presence or absence of hybridizing nucleic acid.

Methods of using probes to identify or differentiate closely related organisms was well known in the art at the time of the invention, as well as manipulations of reaction conditions to increase stringency, as can be exemplified by the teachings in the following references. Hammond teaches hybridization assay probes specific for chlamydia pneumoniae which can distinguish *C. pneumoniae* form its most closely related taxonomic or phylogenetic neighbors (see col. 3, lines 35-40). Hammond teaches obtaining suitable probes for detection and discrimination. Hammond generally teaches that all prokaryotic organisms (except for viruses) contain rRNA genes. Hammond teaches that variable regions of rRNA sequences from the 16S rRNA of *C. pneumoniae* were identified by sequencing the rRNA of *C. pneumoniae* and its closely related phylogenetic neighbors and aligning the sequences to reveal areas of maximum homology and also alignment for regions of sequence variation (col. 3, lines 41-55). For construction of suitable probes, Hammond teaches that first, the stability of the probe:target nucleic acid should be chosen to be compatible with assay conditions, ie: hybridization involving complementary nucleic acids of higher G-C content will be stable at higher temperatures (col. 4, lines 51-65). Hammond teaches that ionic strength and incubation temperature under which a probe will be used, should be taken into account. Hammond teaches that incubation at temperatures below the optimum Tm may allow mismatched base sequences to hybridize and can

therefore result in reduced specificity (col. 5, lines 8-15). Hammond further teaches that it is desirable to have probes which hybridize only under conditions of high stringency.

Hogan also teaches a method for preparing probes for use in qualitative and quantitative assays wherein the probes are capable of detecting and differentiating between eubacteria (see abstract). Hogan also teaches the hybridization of *E. Coli* probes to closely related organisms such as *Shigella boydii, Sh. flexneri, Sh. dysenteriae, and Sh. sonnei* (see col. 52, table 54). Hogan also generally teaches hybridization strategies, including variations in temperature, probe length, probe composition, and ionic strength in methods of identification of target nucleic acids (cols 7-11) and specifically points out that use of temperatures below the optimum (Tm) may allow mismatched base sequences to hybridize and can therefore result in reduced specificity (col. 10, lines 21-24). Hogan also specifically teaches using filter hybridization methods, and the use of rRNA sequences in distinguishing between eubacteria (cols 1 and 2).

Anderson teaches hybridization strategies in constructing probes for methods of screening and identification. Anderson teaches factors affecting the rate of hybridization and the stability of hybrids, (p. 3-13) including probe length, composition, and temperature. Anderson specifically applies these manipulations to filter hybridization. Anderson also specifically teaches that to detect closely related family members, it is better to use stringent hybridization conditions followed by stringent washing conditions (for example, from the teaching of the previous three references, the ordinary artisan would be taught that such a condition could involve high temperature, etc) (p. 13, last sentence).

Dyson teaches that nucleic acid hybridization is an important component of many molecular biology techniques, and that specifically, filter hybridization methods exploit the specificity of molecular hybridization for the detection of rare sequences in a complex mixture (see p. 111, first paragraph). Dyson teaches different methods for immobilization of nucleic acids on filters (pp 111-132) and teaches factors affecting hybridization of nucleic acids (pp 132-151). Dyson teaches that such factors include Tm, base composition, mismatching (p 133), and ionic strength affect hybridization. Dyson teaches that filter hybridization involves three basic steps: pre-hybridization, hybridization, and washing (p. 137, section 3.4). Dyson teaches that after hybridization, the filter is washed to remove the probe. Dyson teaches that short DNA duplexes have a reduced melting temperature and the Tm of oligonucleotide probes can be calculated, although the actual Tm should be determined experimentally (see p 146). Dyson specifically teaches that oligonucleotides are hybridized at a temperature between 5 and 10 degrees below the Tm for 14-48 hours and that filters are then washed four times *at* the hybridization temperature (see p. 147, lines 1-3). Dyson teaches that often, such a wash is enough, however Dyson teaches that if the filters still show considerable activity above background, the wash temperature should be increased by 2-3 °C and the wash should be repeated.

Although neither Hammond, Hogan, Dyson or Anderson teach using the probes of the instant invention, Cilia et al teaches sequence heterogeneities among 16S RNA sequences of E. Coli and Shigella (see abstract, and figure 3) and teaches nucleotide differences among

Eubacteria by showing a line up of regions from 16S genes across species levels, showing the nucleotide sequence similarities and differences. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to construct the DNA sequences of the claimed invention for the use of probes and primers that could distinguish *Shigella* from *E. Coli*. Methods of distinguishing between different eubacteria using probes and primers that target regions of similarity and differences were readily known in the art at the time of the invention and is exemplified by the Hogan patent. The ordinary artisan would have been motivated to construct probes and primers of the claimed invention to identify and differentiate *E.coli* from *Shigella* as Cilia teaches how closely related the two genus of bacteria are (see Fig 1). Cilia et al also teaches the sequences of SEQ ID NOS 1. [Applicant was faxed a copy of the results of a sequence search, which also discloses variants of SEQ ID NO 2, and the complete nucleotide sequence of SEQ ID NOS 1 and 4. This sequence search cites Cilia et al, identified above, as disclosing the accession numbers for these results (see table 1 of Cilia et al).] As the sequences of the 16S rRNA and rDNA sequences of the *Shigella* species and *E.coli* sequences were known at the time of the invention, it would have been obvious for the ordinary artisan to construct probes and primers to regions of variability to be able to differentiate the closely related bacteria. Such methods were readily known in the art as is shown by the large amount of literature available in the art that identifies regions of variability among closely related bacteria for the purpose of constructing probes and primers useful in methods of differentiation.

It would have further been prima facie obvious to one of ordinary skill in the art to raise the temperature of the wash step to achieve maximum specificity and selectivity as Dyson teaches that the temperature of the wash step can be varied by incrementally increasing the temperature. Dyson also provides examples of lengths of probes as well as suggested hybridization and wash temperatures (see table 2, p. 147). In each case, the wash temperature is above the hybridization temperature. Therefore, although Anderson and Dyson teach hybridizing 5-10 degrees *below* the Tm of the probe, Dyson teaches washing above the hybridization temperature and that the wash temperature can be increased by 2-3 degrees. With such a teaching, and the examples in table 2, it would have been readily apparent to one of ordinary skill in the art to increase wash temperatures by 2-3 degrees at a time, and repeat as needed until suitable hybridization had occurred. It would have further been prima facie obvious to one of ordinary skill that because Dyson teaches *suggested* conditions and teaches that manipulations of conditions, such as wash temperature, can be performed to achieve the desired result, a certain amount of manipulation of conditions (such as changing salt concentration, varying temp of both hybridization and washing steps) could be necessary. As the level of skill in the art regarding hybridization of oligonucleotides is very high, the ordinary artisan would have considered that the identification of optimum Tm for washing is a matter of routine optimization and that while one would initially wash at Tm below the Tm of the probe, where such conditions are insufficient to distinguish, the ordinary artisan would know to adjust the conditions, either by increasing the temperature or adjust the buffer (ie: salt concentration).

Response to Arguments

The response traverses the rejection. The response states that collectively, the citations by the examiner fail to teach the use of wash temperatures that exceed the Tm. This argument has been thoroughly reviewed but does not overcome the rejection as the claims are also drawn to washing at the oligonucleotide's calculated or experimentally determined Tm, which is taught by Dyson (see p. 147, lines 8-9) [note: the response acknowledges this teaching by Dyson at page 7 of the response]. Dyson teaches that if filters still show considerable activity above background [when washing at 5-10 degrees below the Tm], the wash temperature should be increased by 2-3 degrees at a time and repeated. Thus, contrary to the assertion in the response, the prior art does teach washing at the Tm. Furthermore, the claim recites "or equivalent wash conditions" which are not defined in the specification, nor does the specification make clear what is considered "equivalent wash conditions".

The response asserts that the examiner may be equating the hybridization temperature with Tm. The examiner has taken this assertion into consideration and respectfully maintains that the examiner has not equated hybridization temperature with the Tm of an oligonucleotide. The response further states that the examiner has not fully disclosed the complete statements of Dyson. The examiner does not understand this point in the response as the examiner is not required to copy the complete disclosure of a reference in a rejection since the examiner is required to provide a complete copy of the reference. The response asserts that the invention of Portugal addresses the need to vigorously wash under conditions that have not previously been

recognized or used. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., prolonged 10 min washes at the Tm) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The examiner acknowledges the response's assertion that Dyson does not specifically teach washing above the Tm of the oligonucleotide.

The response asserts that Hammond fails to teach the fine discrimination between closely related genus and species that is taught in the present invention as well as the washing at or above the Tm. The response asserts that Hogan fails to teach wash temperatures at or above the Tm. The response asserts that Anderson does not recommend washing either at or above the Tm and that Anderson does not suggest any wash conditions. The response asserts that Cilia notes a failure to distinguish species with the sequences discussed in his paper and that anticipatory documents must disclose all the elements of the claim. These arguments have been thoroughly reviewed but were not found persuasive. Firstly, the response has taken each reference cited in the rejection based on 35 USC 103 and attacked them individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). These references, particularly those of Hammond, Hogan, and

Anderson were cited to show the state of the art with regard to hybridization assays. Dyson was cited to also show the state of the art at the time of the invention and further to show that the art was not silent at the time of the invention with regard to washing temperatures relative to a probe's Tm, as the previous responses have repeatedly asserted. With regard to Cilia et al, the reference was cited to show that sequences to Shigella and E. coli were known at the time of the invention. Further, with respect to the rejection made under 35 USC 103, Cilia was not cited as anticipatory, thus the assertion at section 13 d of the response, lines 2-5 is not relevant. The references cited in the rejection based on 35 USC 103 show that it was well within the skill of the ordinary artisan at the time of the invention to construct probes from known sequences to distinguish between different species of organisms and provides the ordinary artisan with the motivation to do so. The combination of references teach adjusting different parameters in a hybridization assay, including temperature, probe content, probe length, and salt concentration to achieve maximum specificity and selectivity. The Dyson reference also specifically teaches adjusting wash conditions by increasing the wash temperature by 2-3 degrees at a time and *repeating*; and also specifically teaches that a wash temperature *at* the probe's Tm can be used.

The response traverses that the publication of the Sabat et al reference proves that the new claims are unobvious and that the examiner must admit the novelty of new art made by skilled practitioners and recognized as novel by those skilled in the art who review submissions prior to publication in scientific journals. This argument has been thoroughly reviewed but was found unpersuasive for reasons already made of record in the previous office action. Further, neither

the MPEP nor the patent laws, to which the examiner is bound, set forth that the novelty or nonobviousness of an invention should be determined based on statements as to such in a scientific journal.

The response asserts that the examiner cites Hogan as not able to distinguish between E. coli and Shigella because Hogan uses different sequences. The inclusion of this statement is not understood however the examiner will address it. In the previous office action the examiner stated that applicants arguments as to the prior art failing to distinguish between E.coli and Shigella was not persuasive because the sequences used by Hogan were different than those used by applicant. The examiner did not state that Hogan could not achieve discrimination because of the use of different sequences, only that because Hogan used different sequences than applicants it was not persuasive with regard to applicants traversal of non obviousness. Further, it is irrelevant as to whether Cilia was available to Hogan in terms of the rejection made under 35 USC 103 as the statute requires that the references be *available to the ordinary artisan at the time the invention was made.*

The office action maintains that while prior art methods do not specifically teach distinguishing between and among E.coli and Shigella, the prior art provides the ordinary artisan with the teaching to carry out applicants invention *as presently claimed.* It was known at the time of the invention that E. coli and Shigella cause different infectious diseases. The prior art provides the sequences of E.coli and Shigella operons. The prior art teaches that detection of a specific organism can be achieved using DNA hybridization assays and teaches how to align

sequences of different species or serotypes to determine areas of sequence variability from which to design probes in a hybridization assay for the purpose of detecting a specific organism. The prior art teaches how to manipulate conditions in a hybridization assay, including temperature of hybridization and wash (see Dyson that teaches washing at the probe's Tm), salt concentration, probe length, and probe content to achieve maximum specificity and selectivity. Thus, the claims *as written* (emphasis added), are not allowable over the prior art.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1655
1/8/02

W. Gary Jones
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